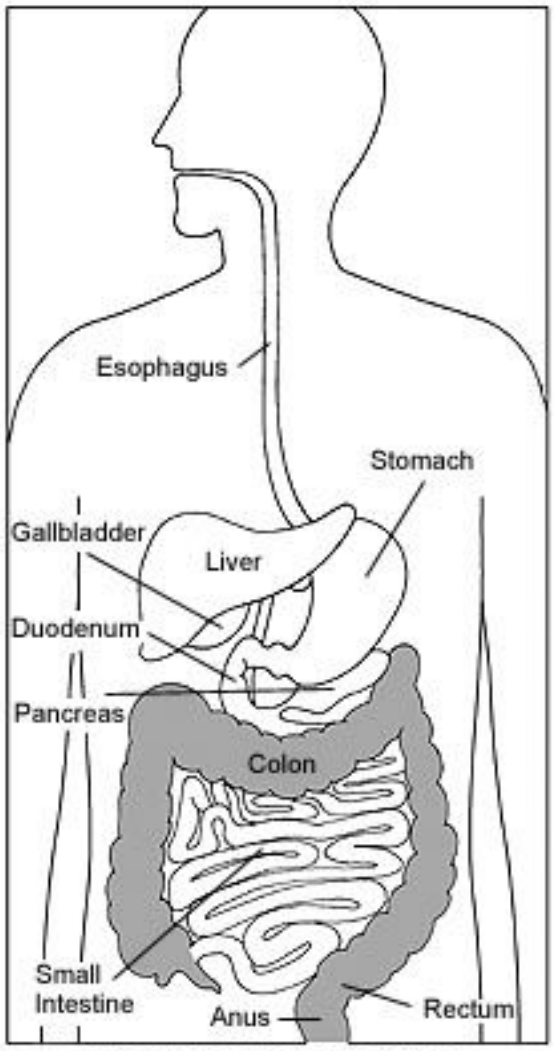
The Digestive System



The human digestive system.

Digestion is the process of turning food into fuel for energy, and for maintenance of the body structure. The digestive tract is a series of hollow organs joined in a long, twisting tube from the mouth to the anus. Inside this tube is a lining called the mucosa. In the mouth, stomach, and small intestine, the mucosa contains tiny glands that produce enzymes to help digest food. There are also two solid digestive organs, the liver and the pancreas, which produce enzymes that reach the intestine through small tubes.

During the digestive process, food passes down the throat, through the esophagus, and into the stomach, where food continues to be broken down. The partially digested food passes into a short tube called the duodenum — the first part of the small intestine. The jejunum and ileum are also part of the small intestine. The liver, the gallbladder, and the pancreas produce enzymes and substances to help with digestion in the small intestine. After the digestive process is complete, the resulting waste travels downstream to the colon. The colon and rectum are parts of the body's digestive system, which removes nutrients from food and stores waste until it passes out of the body. Together, the colon and rectum form a long, muscular tube called the large intestine.

The health of your digestive system has a lot to do with lifestyle — the food you eat, the amount of exercise you get, and the pace and stress level of your day. However, some digestive diseases, such as those discussed here, are thought to be hereditary or stem from an infection. For others, there is no known cause.

Colon Cancer

The American Cancer Society estimates that there will be 93,800 new cases of colon cancer diagnosed in the US in 2000, with 47,700 resulting deaths. All kinds of cancer occur when cell division, normally a very highly regulated process, gets out of control. While environmental factors can certainly contribute to a person's risk of cancer (e.g. smoking, diet, and exercise), most cancers have a genetic basis too. Literally hundreds of genes and proteins are involved in monitoring the process of cell division and DNA replication; a mutation in one or more of these genes or proteins can sometimes lead to uncontrolled cancerous growth.

Colon cancer is one of the most common inherited cancer syndromes known. Among the genes found to be involved in colorectal cancer are: *MSH2* and *MSH6* both on chromosome 2 and *MLH1*, on chromosome 3. Normally, the protein products of these genes help to repair mistakes made in DNA replication. If the MSH2, MSH6, and MLH1 proteins are mutated and therefore don't work properly, the replication mistakes are not repaired, leading to damaged DNA and, in this case, colon cancer.

It is not clear why mutations in genes that are essential in all tissues preferentially cause cancer in the colon. However, studies on the equivalent genes in mice and brewer's yeast are helping to further our understanding of the mechanisms of DNA repair and the role that environmental factors might play in colon cancer incidence.

The human genes mutated in some colon cancers are homologous to enzymes in the DNA mismatch repair pathway in the E. coli bacterium (above) as well as yeast and mice.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=colon%20cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=colon%20cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557761&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=colon%20cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=colon%20cancer] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=colon%20cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

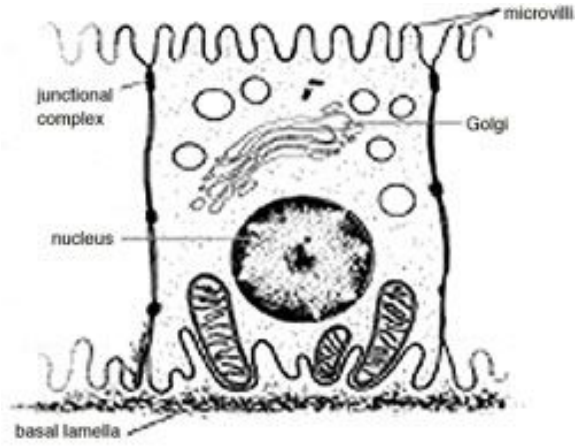
Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

Crohn's Disease

Inflammatory bowel disease (IBD) is a group of chronic disorders that causes inflammation or ulceration in the small and large intestines. Most often, IBD is classified either as ulcerative colitis or Crohn's disease. While ulcerative colitis affects the inner lining of the colon and rectum, Crohn's disease extends into the deeper layers of the intestinal wall. It is a chronic condition and may recur at various times over a lifetime.

About 20% of cases of Crohn's disease appear to run in families. It is a "complex trait," which means that several genes at different locations in the genome may contribute to the disease. A susceptibility locus for the disease was recently mapped to chromosome 16. Candidate genes found in this region include several involved in the inflamatory response, including: CD19, involved in B-lymphocyte function; sialophorin, involved in leukocyte adhesion; the CD11 integrin cluster, involved in microbacterial cell adhesion; and the interleukin-4 receptor, which is interesting, as IL-4-mediated functions are altered in IBDs.

Because some of the genetic factors involved in Crohn's disease may also contribute to ulcerative colitis susceptibility, research into Crohn's disease may assist in further understanding both types of IBD.



Epithelial cells line the intestine and are one of several cell types in the lining of the intestine to be affected in ulcerative colitis or Crohn's disease.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Crohn] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Crohn&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=11545912&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Crohn%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Crohn] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=Crohn] catalog of human genes and disorders

Websites

Fact sheet [www.niddk.nih.gov/health/digest/pubs/crohns/crohns.htm] from the National Institute for Diabetes and Digestive and Kidney Diseases, NIH

The Crohn's disease web page [www.healingwell.com/ibd/] information and links

The Crohn's and colitis pharmacist [www.CrohnsPharmacist.com] disease and medication information

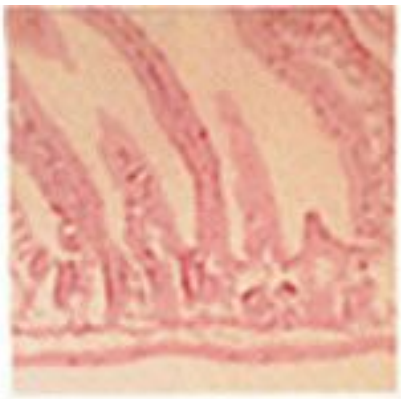
MEDLINE*plus* [www.nlm.nih.gov/medlineplus/crohnsdisease.html] links on Crohn's disease compiled by the National Library of Medicine

Cystic Fibrosis

Cystic fibrosis (CF) is the most common fatal genetic disease in the US today. It causes the body to produce a thick, sticky mucus that clogs the lungs, leading to infection, and blocks the pancreas, stopping digestive enzymes from reaching the intestines where they are required to digest food.

CF is caused by a defective gene, which codes for a sodium and chloride (salt) transporter found on the surface of the epithelial cells that line the lungs and other organs. Several hundred mutations have been found in this gene, all of which result in defective transport of sodium and chloride by epithelial cells. The severity of the disease symptoms of CF is directly related to the characteristic effects of the particular mutation(s) that have been inherited by the sufferer.

CF research has accelerated sharply since the discovery of CFTR in 1989. In 1990, scientists successfully cloned the normal gene and added it to CF cells in the laboratory, which corrected the defective sodium chloride transport mechanism. This technique—gene therapy—was then tried on a limited number of CF patients. However this treatment may not be as successful as originally hoped. Further research will be required before gene therapy, and other experimental treatments, prove useful in combating CF.



Building mouse models of human disease. Expression of a human cystic fibrosis (CFTR) gene in the gut of a mouse. A human anti-sense probe was used to show human CFTR expressed in the mouse duodenem. [Reproduced with permission from Manson, A.L. et al. (1997) EMBO J. 16, 4238-4249.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=cystic%20fibrosis] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=cystic%20fibrosis&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6995996&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=cystic%20fibrosis%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=cystic%20fibrosis] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=cystic%20fibrosis] catalog of human genes and disorders

Websites

Fact sheet [www.nhlbi.nih.gov/health/public/lung/other/cystfib.htm] from the National Heart, Lung and Blood Institute, NIH

The Cystic Fibrosis Foundation [www.cff.org/] information and links

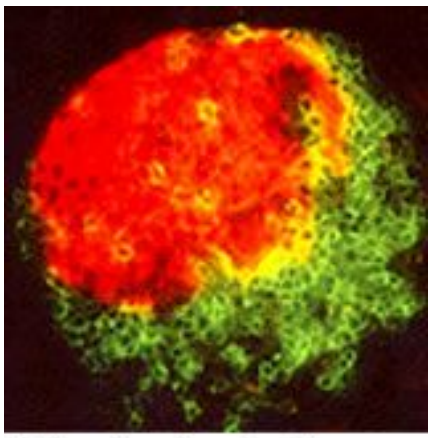
Diabetes, Type 1

Diabetes is a chronic metabolic disorder that adversely affects the body's ability to manufacture and use insulin, a hormone necessary for the conversion of food into energy. The disease greatly increases the risk of blindness, heart disease, kidney failure, neurological disease, and other conditions for the approximately 16 million Americans who are affected by it. Type 1, or juvenile onset diabetes, is the more severe form of the illness.

Type 1 diabetes is what is known as a 'complex trait', which means that mutations in several genes likely contribute to the disease. For example, it is now known that the insulin-dependent diabetes mellitus (IDDM1) locus on chromosome 6 may harbor at least one susceptibility gene for Type 1 diabetes. Exactly how a mutation at this locus adds to patient risk is not clear, although a gene maps to the region of chromosome 6 that also has genes for antigens (the molecules that normally tell the immune system not to attack itself). In Type 1 diabetes, the body's immune system mounts an immunological assault on its own insulin and the pancreatic cells that manufacture it. However, the mechanism of how this happens is not yet understood.

About 10 loci in the human genome have now been found that seem to confer susceptibility to Type 1 diabetes. Among these are 1) a gene at the locus IDDM2 on chromosome 11 and 2) the gene for glucokinase (GCK), an enzyme that is key to glucose metabolism which helps modulate insulin secretion, on chromosome 7.

Conscientious patient care and daily insulin dosages can keep patients comparatively healthy. But in order to prevent the immunoresponses that often cause diabetes, we will need to experiment further with mouse models of the disease and advance our understanding of how genes on other chromosomes might add to a patient's risk of diabetes.



T lymphocytes attacking insulin-producing pancreatic islet cells.[Image credit: A. Cooke and John Todd, Wellcome Trust Center for Human Genetics, Oxford, UK.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=diabetes+NOT+morbid] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=diabetes&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=diabetes%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=diabetes] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=diabetes] catalog of human genes and disorders

Websites

Patient information on diabetes [www.niddk.nih.gov/health/diabetes/diabetes.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Juvenile Diabetes Foundation [www.jdfcure.com] 'creating a world without diabetes'

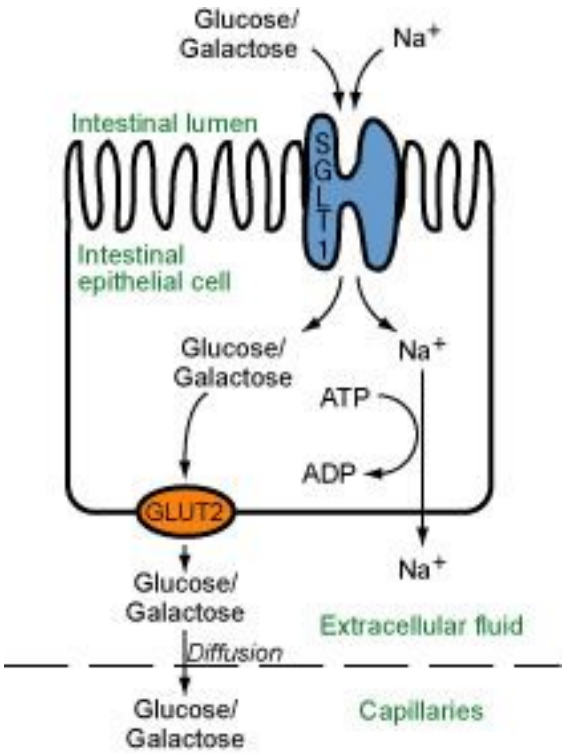
American Diabetes Association [www.diabetes.org/default.htm] research and information

Glucose Galactose Malabsorption

Glucose Galactose Malabsorption (GGM) is a rare metabolic disorder caused by a defect in glucose and galactose transport across the intestinal lining. GGM is characterized by severe diarrhea and dehydration as early as the first day of life and can result in rapid death if lactose (milk sugar), sucrose (table sugar), glucose, and galactose are not removed from the diet. Half of the 200 severe GGM cases found worldwide result from familial intermarriage. At least 10% of the general population has glucose intolerance, however, and it is possible that these people may have milder forms of the disease.

GGM is an autosomal recessive disorder in which affected individuals inherit two defective copies of the *SGLT1* gene, located on chromosome 22. Normally within the space enclosed by the small intestine (called the lumen), lactose is broken down into glucose and galactose by an enzyme called lactase, while sucrose is broken down into glucose and fructose by an enzyme called sucrase. The protein product of *SGLT1* then moves the glucose and the galactose from the lumen of the small intestine into intestinal cells. Usually the mutations carried by GGM individuals result in nonfunctional truncated SGLT1 proteins or in the improper placement of the proteins such that they can not transport glucose and galactose out of the intestinal lumen. The glucose and galactose, if left untransported, draw water out of the body into the intestinal lumen, resulting in diarrhea.

Although no cure exists for GGM, patients can control their symptoms (diarrhea) by removing lactose, sucrose, and glucose from their diets. Infants showing a prenatal diagnosis of GGM will thrive on a fructose-based replacement formula and will later continue their "normal" physical development on a fructose-based solid diet. Older children and adults with severe GGM can also manage their symptoms on a fructose-based diet and may show improved glucose tolerance and even clinical remission as they age.



Co-transport of sodium and glucose or galactose by SGLT1. For every two sodium ions SGLT1 moves inside the cell down the sodium concentration gradient, one glucose or galactose molecule moves with it. The glucose/galactose is then transported into the extracellular fluid by GLUT2, and diffuses into the capillaries. Sodium is actively transported out of the cell into the intercellular space so as to maintain the intracellular sodium concentration gradient.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=SGLT1] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=SGLT1&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5730021&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=SGLT1%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=SGLT1] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=182380] catalog of human genes and disorders

Websites

National Organization For Rare Disorders [www.stepstn.com/cgi-win/nord.exe?proc=Redirect&type=rdb_sum&id=749.htm] nonprofit organization

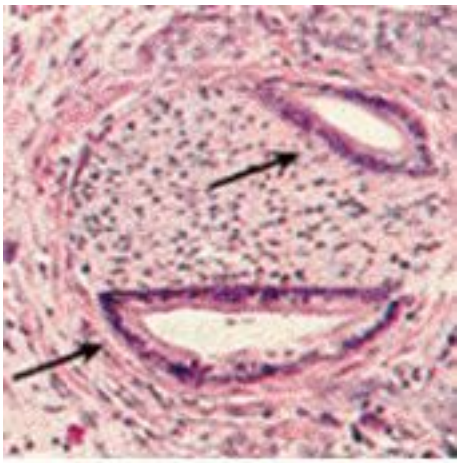
National Digestive Diseases Information Clearinghouse [www.niddk.nih.gov/health/digest/nddic.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Pancreatic Cancer

The pancreas is responsible for producing the hormone insulin, along with other substances. It also plays a key role in the digestion of protein. There were an estimated 27,000 new cases of pancreatic cancer in the US in 1997, with 28,100 deaths from the disease.

About 90% of human pancreatic carcinomas show a loss of part of chromosome 18. In 1996, a possible tumor suppressor gene, DPC4 (Smad4), was discovered from the section that is lost in pancreatic cancer, so may play a role in pancreatic cancer. There is a whole family of Smad proteins in vertebrates, all involved in signal transduction of transforming growth factor β (TGFβ) related pathways. Other tumor suppressor genes include p53 and Rb, which, if mutated or absent from the genome can contribute to cancerous growth in a variety of tissues.

DPC4 (Smad4) homologs exist in the worm (*Caenorhabditis elegans*), mouse and the fly (*Drosophila*). In *Drosophila*, when the gene is not present, there a number of developmental defects. Likewise, homozygous Smad4 mutant mouse embryos die before embryonic day 7.5, and have reduced size because of reduced cell proliferation. Research on these model organisms should help elucidate the role of Smad4 and related proteins in humans.



Loss of DPC4 (Smad4) gene causes pancreatic cancers to grow aggressively, as seen by tumor cells invading a nerve bundle. [Image credit: R.H. Hruban, Johns Hopkins University, Baltimore, MD, USA. Reprinted from SCIENCE, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=pancreatic+cancer] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=pancreatic+cancer&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4885457&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=pancreatic+cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=pancreatic+cancer] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=pancreatic%20cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

American Cancer Society [www.cancer.org] research and patient support

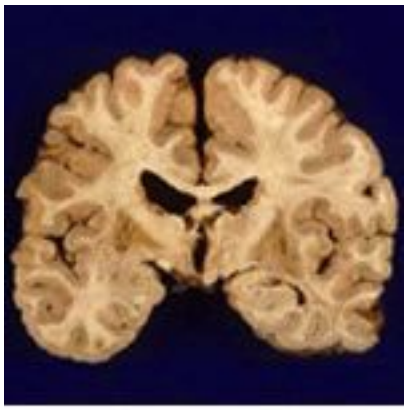
MEDLINE*plus* [www.nlm.nih.gov/medlineplus/pancreaticcancer.html] links on pancreatic cancer compiled by the National Library of Medicine

Wilson's Disease

Wilson's Disease is a rare autosomal recessive disorder of copper transport, resulting in copper accumulation and toxicity to the liver and brain. Liver disease is the most common symptom in children; neurological disease is most common in young adults. The cornea of the eye can also be affected: the 'Kayser-Fleischer ring' is a deep copper-colored ring at the periphery of the cornea, and is thought to represent copper deposits.

The gene for Wilson's disease (ATP7B) was mapped to chromosome 13. The sequence of the gene was found to be similar to sections of the gene defective in Menkes disease, another disease caused by defects in copper transport. The similar sequences code for copper-binding regions, which are part of a transmembrane pump called a P-type ATPase that is very similar to the Menkes disease protein.

A homolog to the human ATP7B gene has been mapped to mouse chromosome 8, and an authentic model of the human disease in rat is also available (called the Long-Evans Cinnamon [LEC][rat). These systems will be useful for studying copper transport and liver pathophysiology, and should help in the development of a therapy for Wilson disease.



In Wilson's disease, toxic levels of copper accumulate and damage many tissues and organs, including the basal ganglia of the brain. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=ATP7B] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=ATP7B&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502323&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=ATP7B%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=ATP7B] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=277900] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/wilsons_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

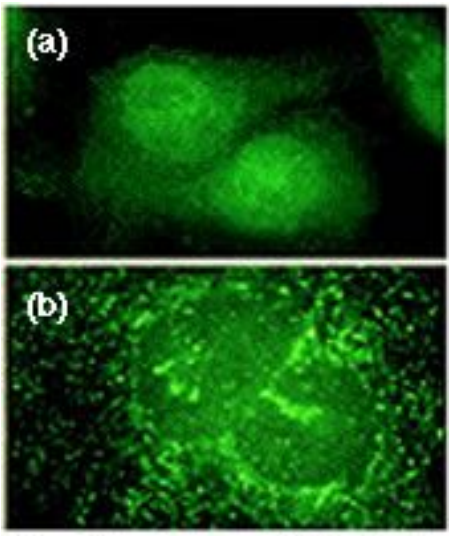
GeneClinics [www.geneclinics.org/profiles/wilson/] a medical genetics resource

Zellweger Syndrome

Zellweger syndrome is a rare hereditary disorder affecting infants, and usually results in death. Unusual problems in prenatal development, an enlarged liver, high levels of iron and copper in the blood, and vision disturbances are among the major manifestations of Zellweger syndrome.

The PXR1 gene has been mapped to chromosome 12; mutations in this gene cause Zellweger syndrome. The PXR1 gene product is a receptor found on the surface of peroxisomes - microbodies found in animal cells, especially liver, kidney and brain cells. The function of peroxisomes is not fully understood, although the enzymes they contain carry out a number of metabolically important reactions. The PXR1 receptor is vital for the import of these enzymes into the peroxisomes: without it functioning properly, the peroxisomes can not use the enzymes to carry out their important functions, such as cellular lipid metabolism and metabolic oxidations.

There is a yeast homolog to human PXR1, which should allow powerful molecular genetic techniques to be used in the investigation of the normal role of peroxisomes in cells, as well as the molecular events that occur in disease states.



Peroxisomes are not detected in Zellweger syndrome fibroblasts (a), but can be reconstituted by transfection with PXR1 gene (b). [Image credit: Nancy Braverman, Gabrielle Dodt, Hugo Moser, Stephen Gould and David Valle, Johns Hopkins UNiversity, Baltimore, MD, USA.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=zellweger] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=zellweger&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506347&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=zellweger%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=zellweger] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600414] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/zellwege_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH